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KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK,
MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL,
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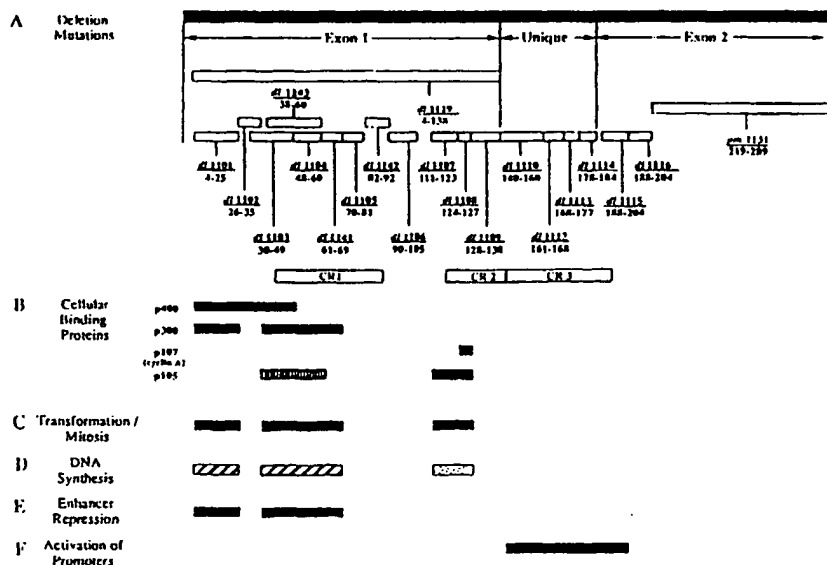
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MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM,
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RECOMBINANT E1A DELETED ADENOVIRAL VECTORS



(57) Abstract: The present invention is directed to recombinant adenoviral vectors capable of replication under particular host cell conditions. In particular, the present invention provides adenoviruses containing modifications to the E1a region which have therapeutic and diagnostic applications. The vectors of the present invention are capable of replication and lysis of neoplastic cells. The vectors may optionally include modifications to the genome so as to impart specific replicative or targeting functions. The present invention also provides pharmaceutical formulations of such vectors. The present invention further provides methods of use of such vectors. The present invention further provides methods of preparing the vectors

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/21451

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/34 C12N15/861 C07K14/075 A61K48/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	<p>WO 94 18992 A (ONYX PHARMACEUTICALS) 1 September 1994 (1994-09-01) page 4, line 23-38</p> <p>page 6, line 4-25 page 17, line 24-37; figure 1 page 18, line 1-9 page 18, line 35 -page 19, line 11 page 28, line 12 -page 31, line 11 example 1 claims 1-3,5,7-10,13,14,16 ---</p> <p style="text-align: center;">-/--</p>	<p>1,8-12, 17 2-5,7, 13,14,16</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

18 August 2000

Date of mailing of the international search report

13. 09. 2000

Name and mailing address of the ISA

Authorized officer

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/21451

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>HOWE J A ET AL.: "Retinoblastoma growth suppressor and a 300-kDa protein appear to regulate cellular DNA synthesis" PROC. NATL. ACAD. SCI. USA, vol. 87, August 1990 (1990-08), pages 5883-5887, XP002134798 abstract figure 1; table 1 page 5886, right-hand column, line 27-40</p> <p>---</p>	2-5,7, 13,14,16
Y	<p>BARBEAU D ET AL.: "Functional interactions within adenovirus E1A protein complexes" ONCOGENE, vol. 9, no. 2, February 1994 (1994-02), pages 359-373, XP000891798 abstract figure 5; table 1</p> <p>---</p>	2,4,5, 13,14
A	<p>JELSMA T N ET AL.: "Use of deletion and point mutants spanning the coding region of the adenovirus 5 E1A gene to define a domain that is essential for transcriptional activation" VIROLOGY, vol. 163, no. 2, April 1988 (1988-04), pages 494-502, XP000891615 cited in the application abstract figure 2; table 1</p> <p>---</p>	1,2,4,13
A	<p>BAYLEY S T ET AL.: "Adenovirus E1A proteins and transformation (Review)" INTERNATIONAL JOURNAL OF ONCOLOGY, vol. 5, no. 3, September 1994 (1994-09), pages 425-444, XP000877368 cited in the application abstract figure 1</p> <p>-----</p>	1

INTERNATIONAL SEARCH REPORT

Int. application No.
PCT/US 99/21451

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-11 (as far as they concern or are related to in vivo methods) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,8-12,17 (all partially); 2,4,5,13, 14 (all completely)

A method of ablating neoplastic cells in a population of normal cells contaminated by neoplastic cells, by the administration to said population of cells a selectively replicating recombinant adenovirus which contains modifications to the Ela coding sequence so as to produce Ela gene products which are deficient in binding to one or more p300 protein family members and to one or more retinoblastoma (pRb) protein family members, but expresses a modified 289R protein retaining the transactivating function of the Ela CR3 domain, said adenoviral vector containing a deletion corresponding to the amino acids 4-25 of the Ela 243R and 289R proteins, preferably comprising a further deletion corresponding to amino acids 111-123 or to amino acids 124-127 of said proteins. Also claimed are further administration methods, and pharmaceutical formulations comprising said adenoviral vectors.

2. Claims: 1,8-12,17 (all partially); 3,6,7,15, 16 (all completely)

A method of ablating neoplastic cells in a population of normal cells contaminated by neoplastic cells, by the administration to said population of cells a selectively replicating recombinant adenovirus which contains modifications to the Ela coding sequence so as to produce Ela gene products which are deficient in binding to one or more p300 protein family members and to one or more retinoblastoma (pRb) protein family members, but expresses a modified 289R protein retaining the transactivating function of the Ela CR3 domain, said adenoviral vector containing a deletion corresponding to the amino acids 38-60 of the Ela 243R and 289R proteins, preferably comprising a further deletion corresponding to amino acids 111-123 or to amino acids 124-127 of said proteins. Also claimed are further administration methods, and pharmaceutical formulations comprising said adenoviral vectors.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/21451

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9418992 A	01-09-1994	AT 178490 T	15-04-1999
		AU 682854 B	23-10-1997
		AU 6272294 A	14-09-1994
		CA 2152941 A	01-09-1994
		DE 69417734 D	12-05-1999
		DE 69417734 T	07-10-1999
		EP 0689447 A	03-01-1996
		EP 0931830 A	28-07-1999
		ES 2134346 T	01-10-1999
		GR 3030385 T	30-09-1999
		JP 8507076 T	30-07-1996
		US 5972706 A	26-10-1999
		US 5801029 A	01-09-1998
		US 5846945 A	08-12-1998
		US 5677178 A	14-10-1997
		US 5856181 A	05-01-1999
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